Relapsed Aggressive B-cell NHL: CAR-T vs Bispecific Antibodies

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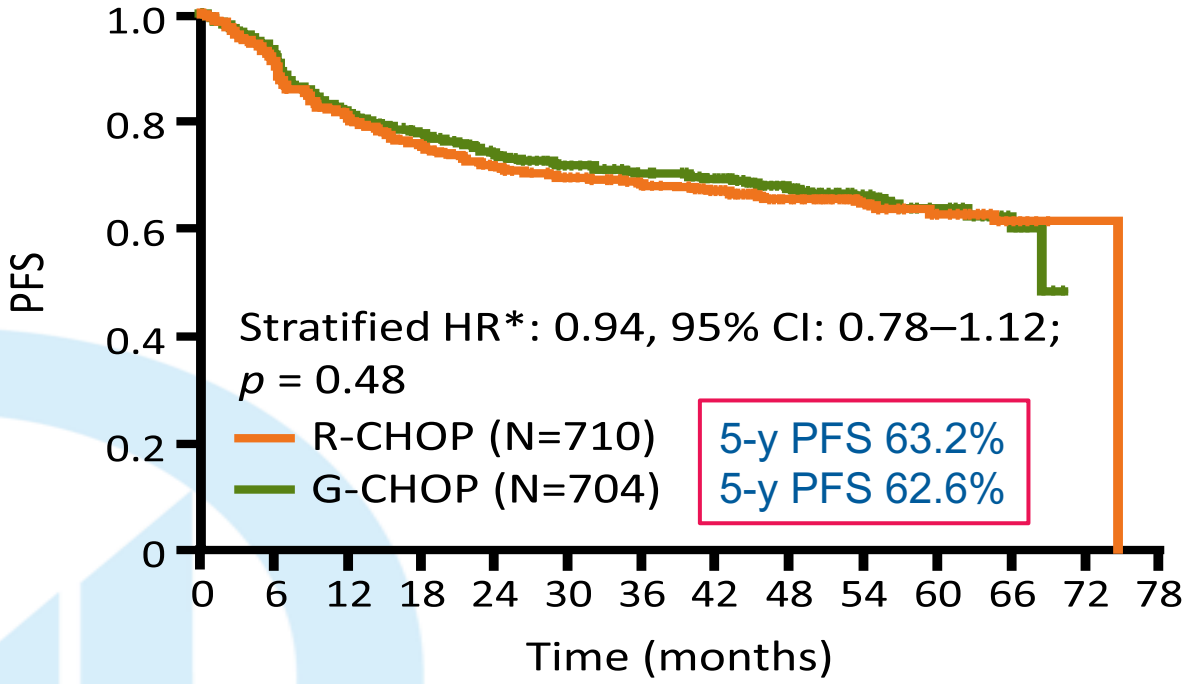
Outcomes Frontline Therapy DLBCL: 5-year Analysis GOYA trial



Sehn L et al., J Hem Oncol 2020

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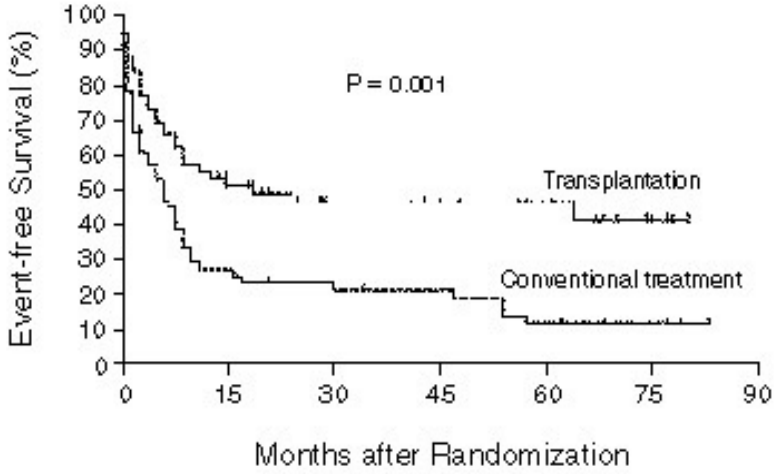
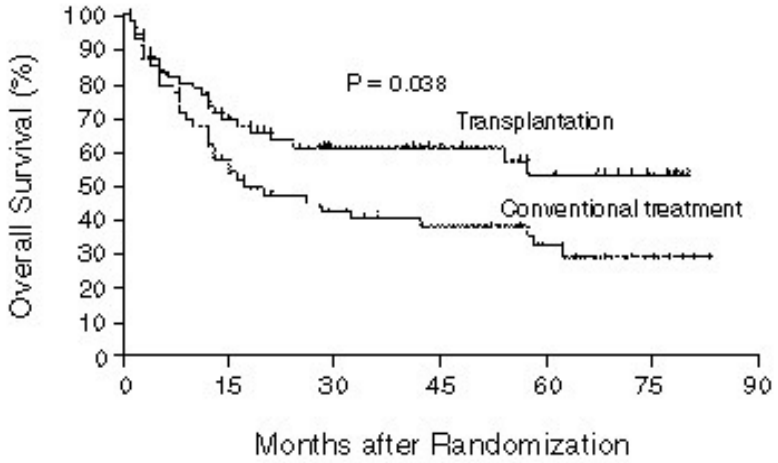
Autologous HCT as Standard Care for R/R DLBCL





Philip et al., NEJM 1995

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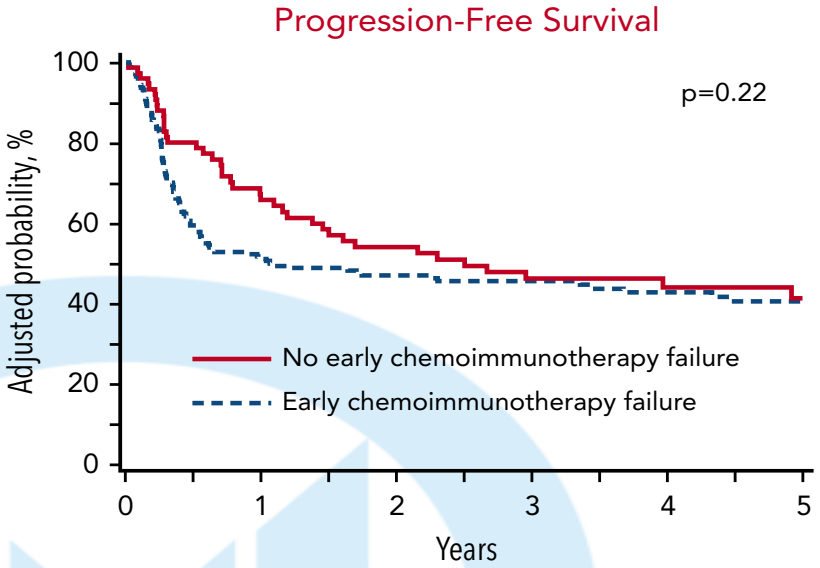
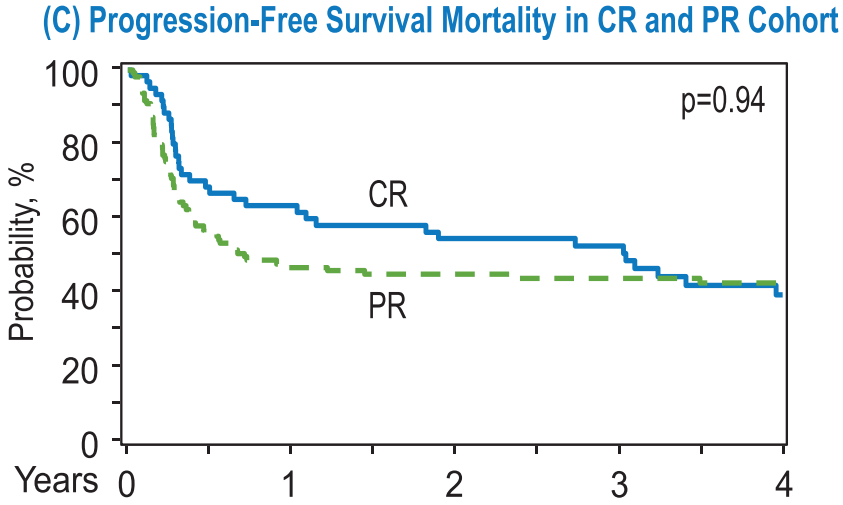
Autologous HCT is still beneficial in chemosensitive disease despite timing of relapse: CIBMTR Analysis





Shah N et al. Blood 2021; Bal S et al;. Trans Cell Ther 2021

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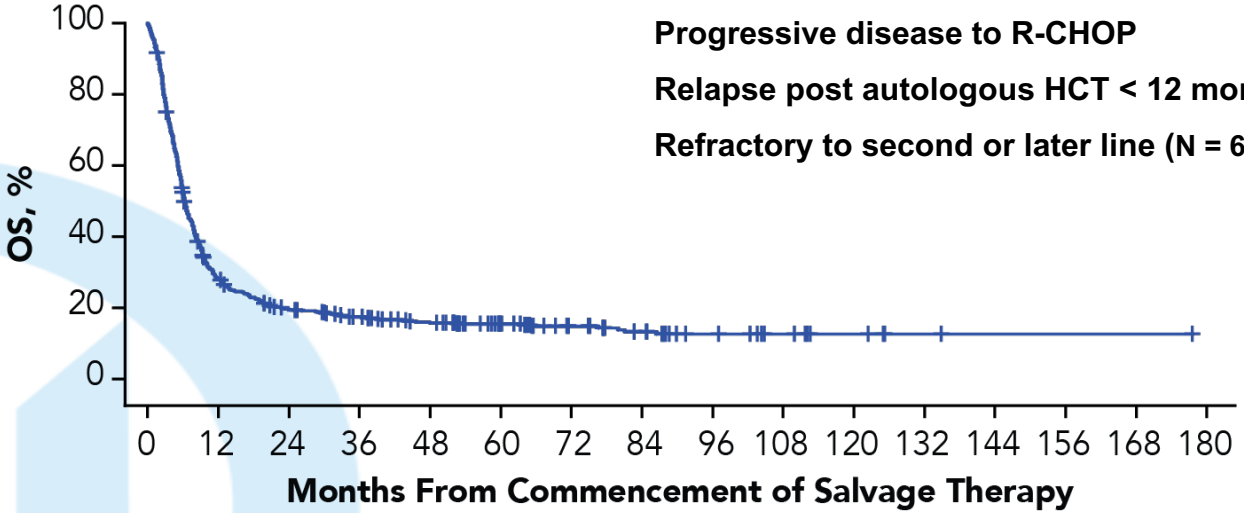
Refractory Diffuse Large B cell Lymphoma carries a poor prognosis

- SCHOLAR-1 patient level meta-analysis of refractory Aggressive NHL
  - ORR of 26% (CR of 7%, PR of 19%)
  - **Median OS of 6.6 months**



Progressive disease to R-CHOP

Relapse post autologous HCT < 12 months-

Refractory to second or later line (N = 636)

Crump M, et al. *Blood.* 2017; blood-2017-03-769620.

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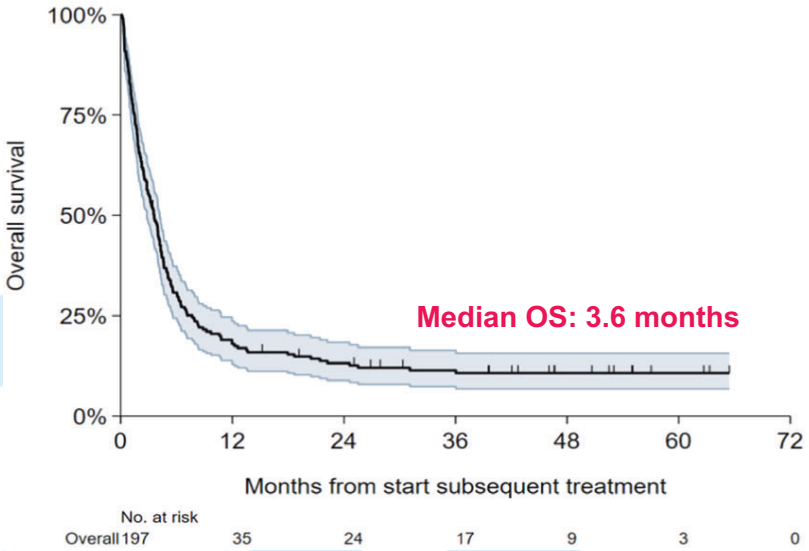
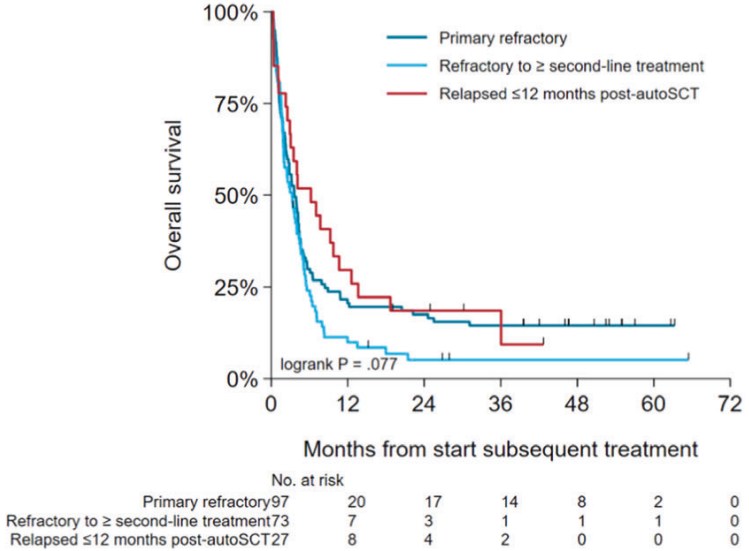
Real-Life R/R DLBCL: Population Based Analysis-Netherlands





Pennings E et Al. B Can Journ 2023

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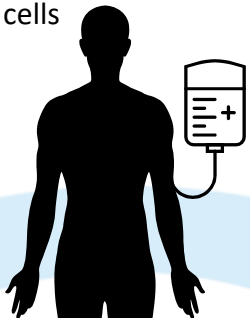
CAR T-Cell Therapy: Underlying Principles

Leukapheresis

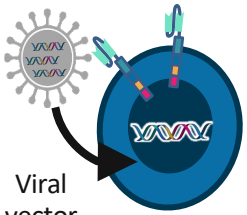
Collect patient's white blood cells

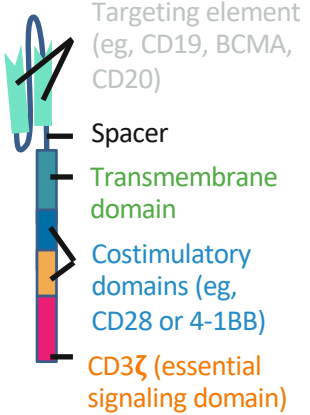


Manufacturing

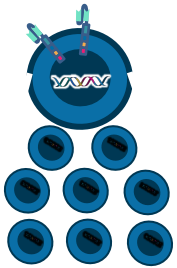
Isolate and activate T-cells

Engineer T-cells with CAR gene





Expand CAR T-cells

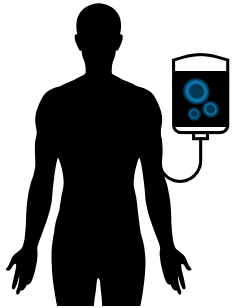


Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

Infusion

Infuse same patient with CAR T-cells



Activity

Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

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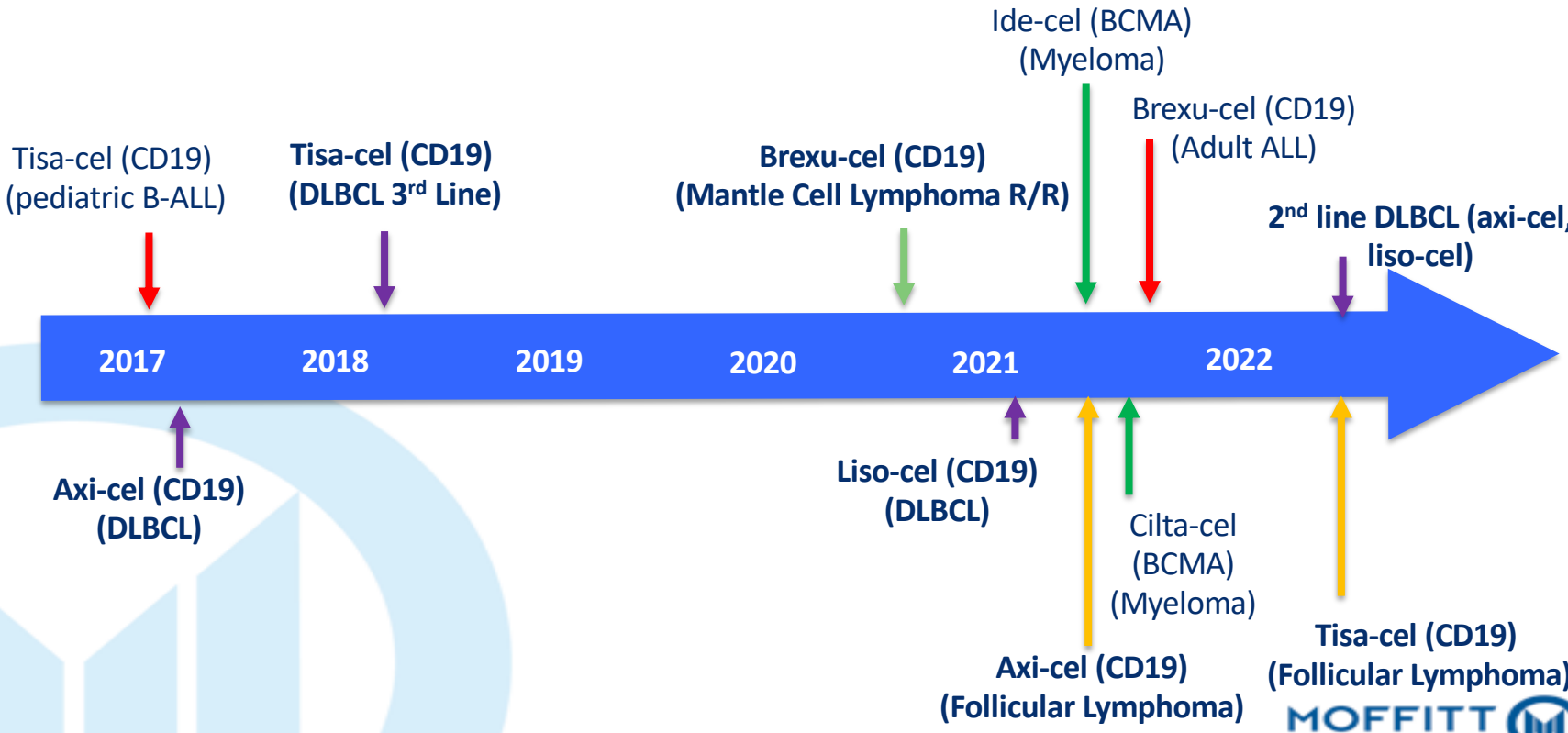
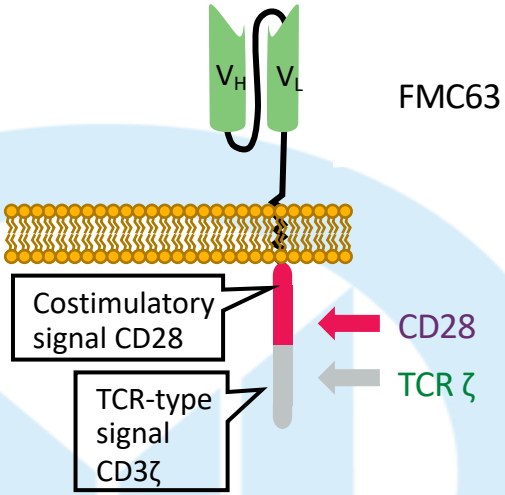
US FDA approvals of CAR T therapy



CD19-Directed CAR T-Cell Products for LBCL

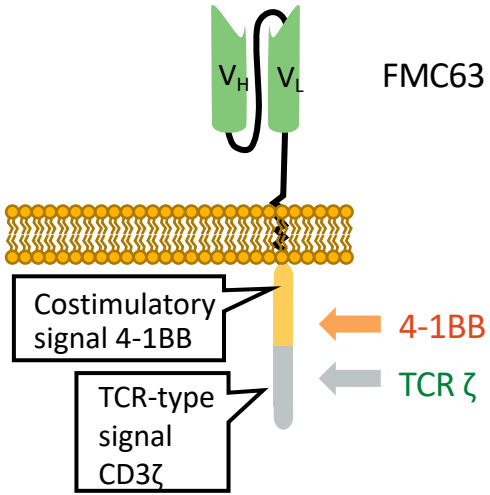
Axicabtagene Ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



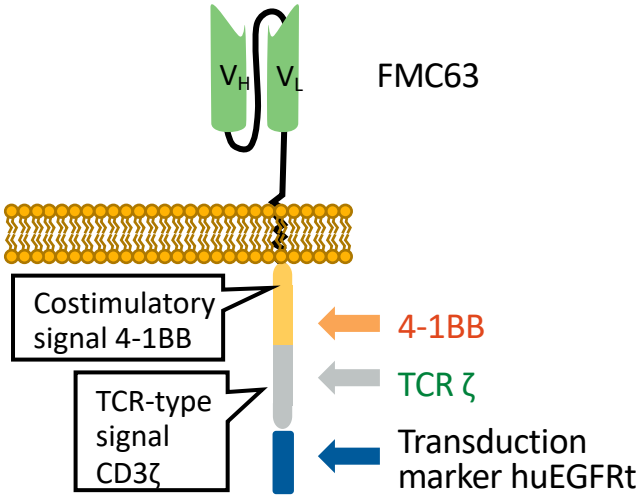
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene Maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



van der Stegen. Nat Rev Drug Discov. 2015;14:499.

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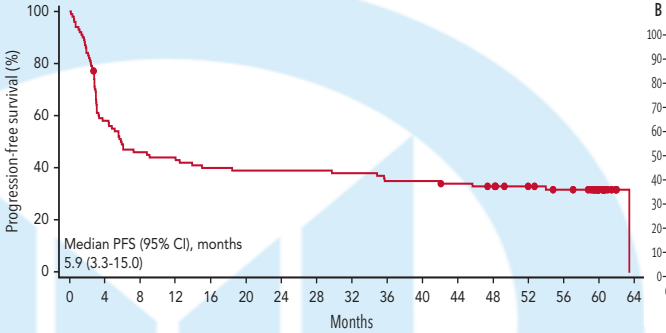
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: Long term follow-up

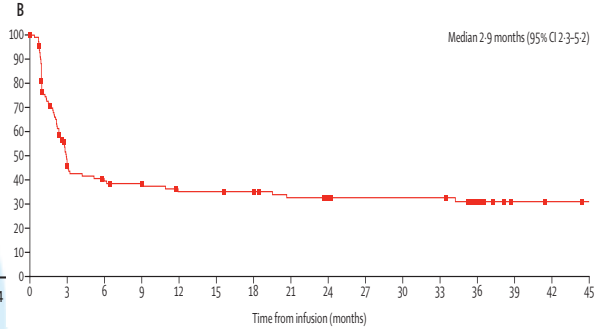
ZUMA-1
Axicabtagene Ciloleucel

Median F/U 5 years
Median age: 58 (23 – 76)
Enrolled (treated): 111 (101)
Best ORR: 83%
Best CR: 54%
PFS: 5.9 months
Ongoing CR: 39%



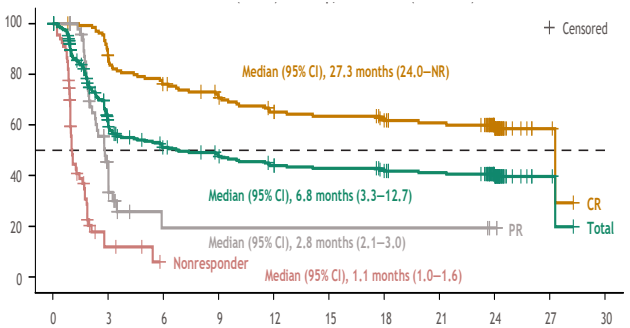
JULIET
Tisagenlecleucel

Median F/U 40.3 months
Median age: 56 (22 – 76)
Enrolled (treated): 165 (111)
Best ORR: 52%
Best CR: 40 %
PFS: 2.9 months
Ongoing CR: 37%



TRANSCEND NHL 001
Lisocabtagene Maraleucel

Median F/U 24 months
Median age: 63 (18 – 86)
Enrolled (treated): 244 (269)
Best ORR: 73%
Best CR: 53 %
PFS: 6.8 months
Ongoing CR: 45%



Neelapu et Al. Blood 2023. Schuster et Al. Lancet Oncol 2021. Abramson et Al. Blood 2023

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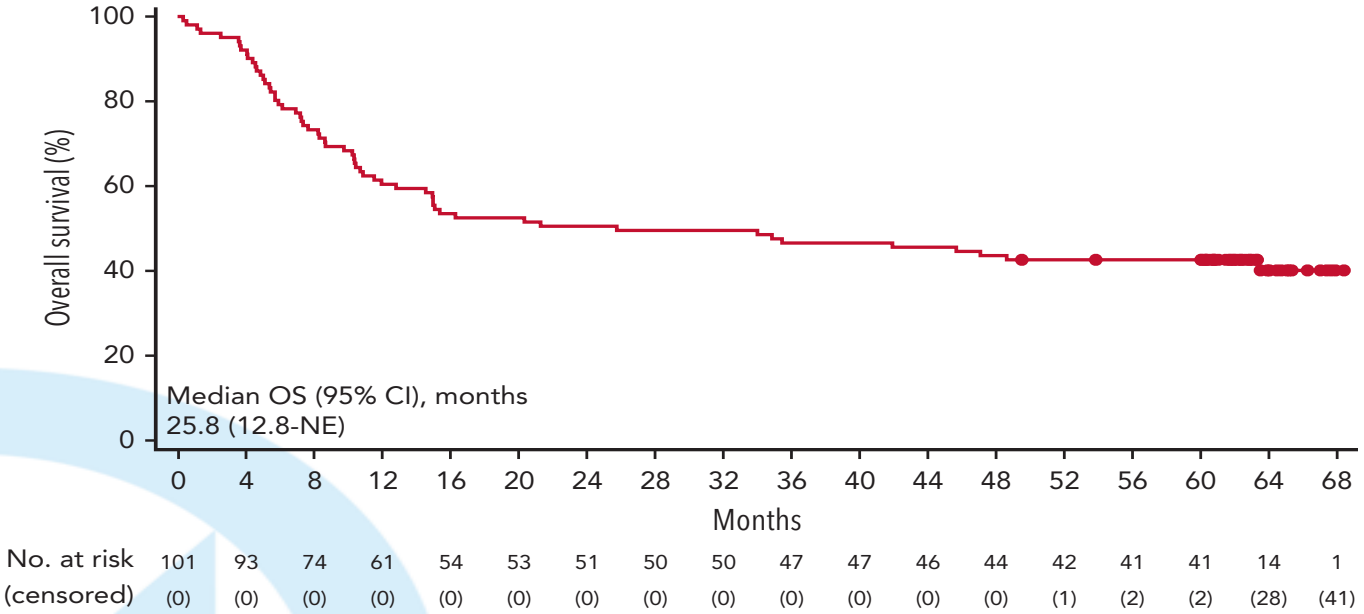
ZUMA-1: Long term efficacy of Axi-Cel in R/R DLBCL-Overall Survival Update At 5 Years (mITT, n = 101): Curative potential



- With ≥ 5 years of follow-up, median OS was 25.8 months, and the KM estimate of the 5-year OS rate was 42.6%
- Since the 4-y cut-off there was 1 dead (month 63) and 1 PD (month 54)

Jacobson et al. ASH Meeting 2021: 1760, Neelapu et al. Blood 2023

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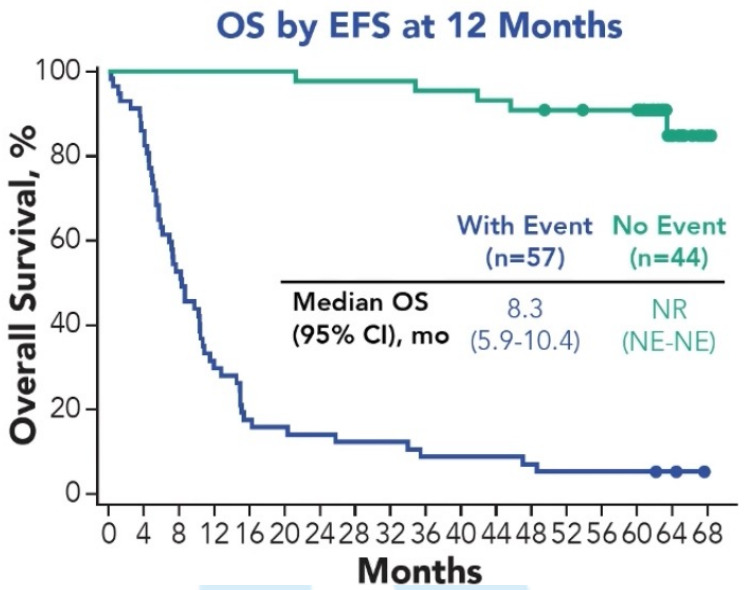
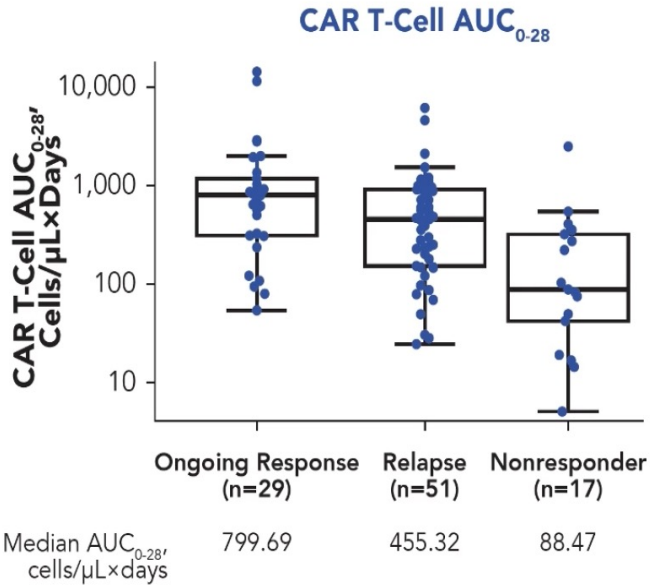
ZUMA-1: OS by event at 12 months and ongoing response by CART expansion





Jacobson et al. ASH Meeting 2021: 1760; Neelapu et al. Blood 2023

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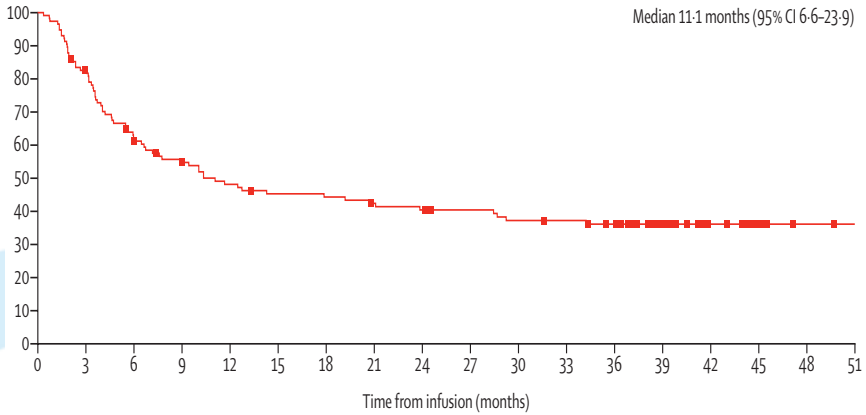
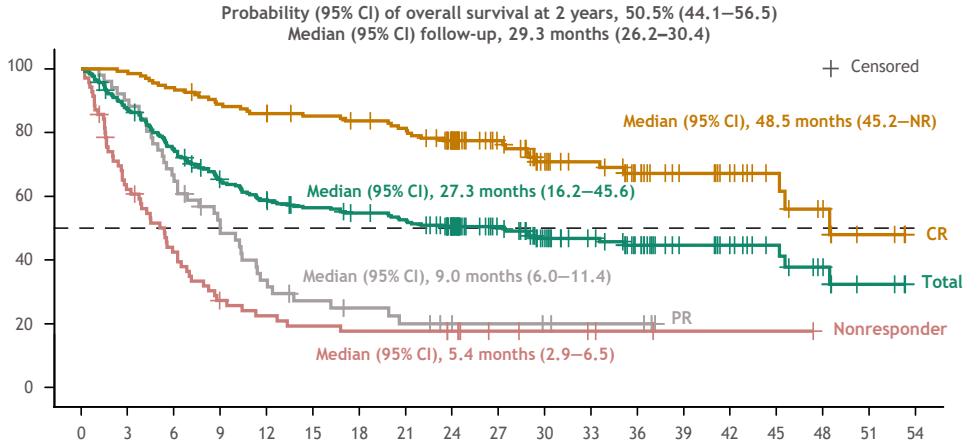
OS update in JULIET (Tisa-Cel) and TRANSCEND (Liso_cel)

JULIET



Median follow up: 40.3 months

TRANSCEND



Median follow up: 23.9 months

Schuster S et al. *Lancet Oncol* 2021; Abramson et Al. *Blood* 2023

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The quest to cure more patients with R/R DLBCL

ZUMA-7
Axicabtagene ciloleucel

Locke et al ASH Meeting 2021 Abstract 2

Met endpoint

BELINDA
Tisagenlecleucel

High-risk DLBCL/B-cell lymphomas:
- Refractory to first-line tx
- Relapsed after first-line tx

TRANSFORM
Lisocabtagene maraleucel

Mandar et al ASH Meeting 2021 Abstract 91

Met endpoint

CAR T-cell therapy

Salvage therapy/ auto-transplant

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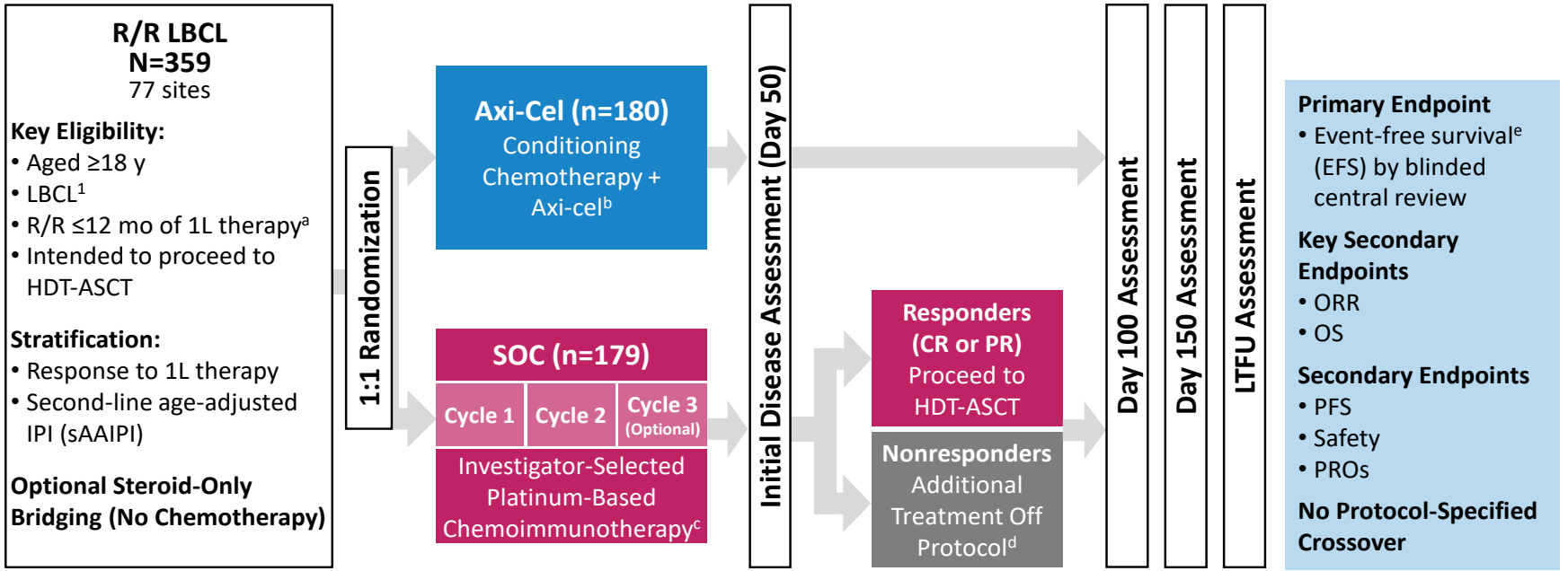
ZUMA-7: Axi-Cel vs SOC Study Schema



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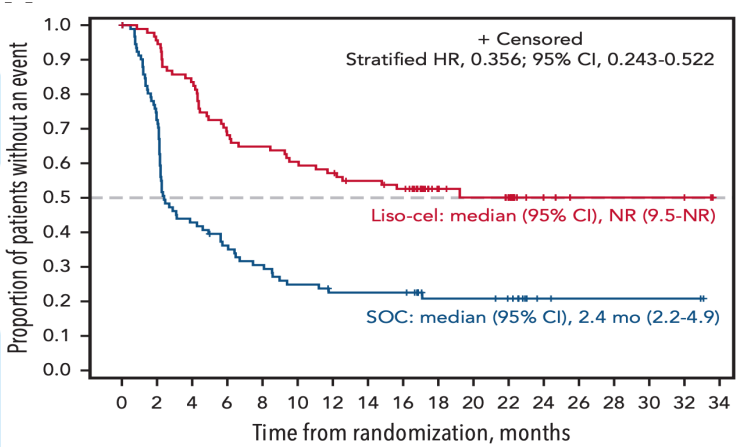
Phase III randomized trials in transplant eligible: EFS and PFS results

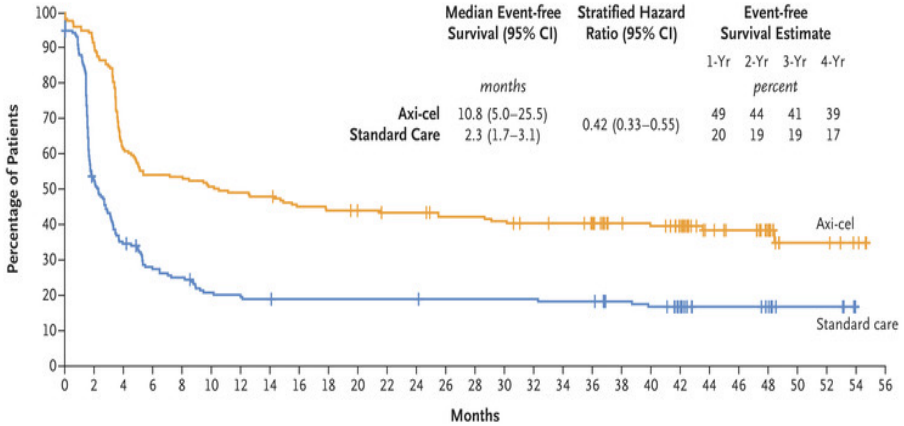
TRANSFORM
Lisocabtagene maraleucel vs SOC

Median F/U: 24.9 months
Median age: 60 (20 – 74)
Enrolled (CAR-T) 92
Best ORR: 87%
Best CR: 74%
PFS: NR



ZUMA-7
Axicabtagene Ciloleucel vs SOC

Median F/U 47.2 months
Median age: 58 (21 – 80)
Enrolled (CAR-T): 180
Best ORR: 83%
Best CR: 65%
PFS: 14.7 months



Abramson et al. Blood 2023; Locke et al. NEJM 2021

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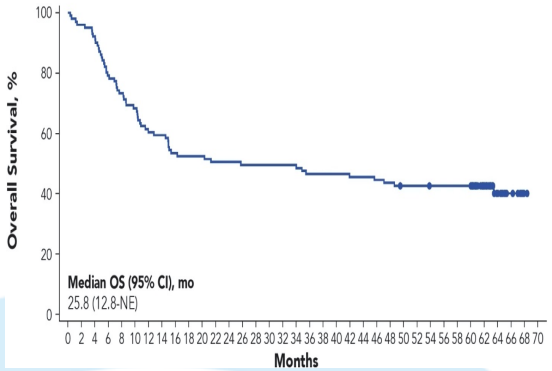
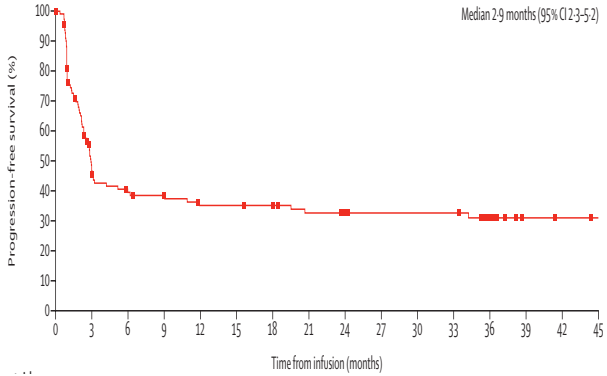
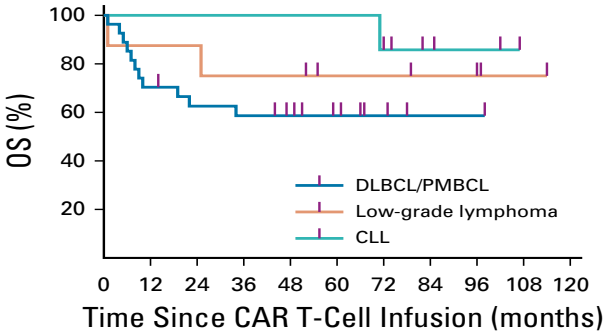
Patients with R/R DLBCL are cured with CAR-T



ZUMA-1



JULIET



NCI

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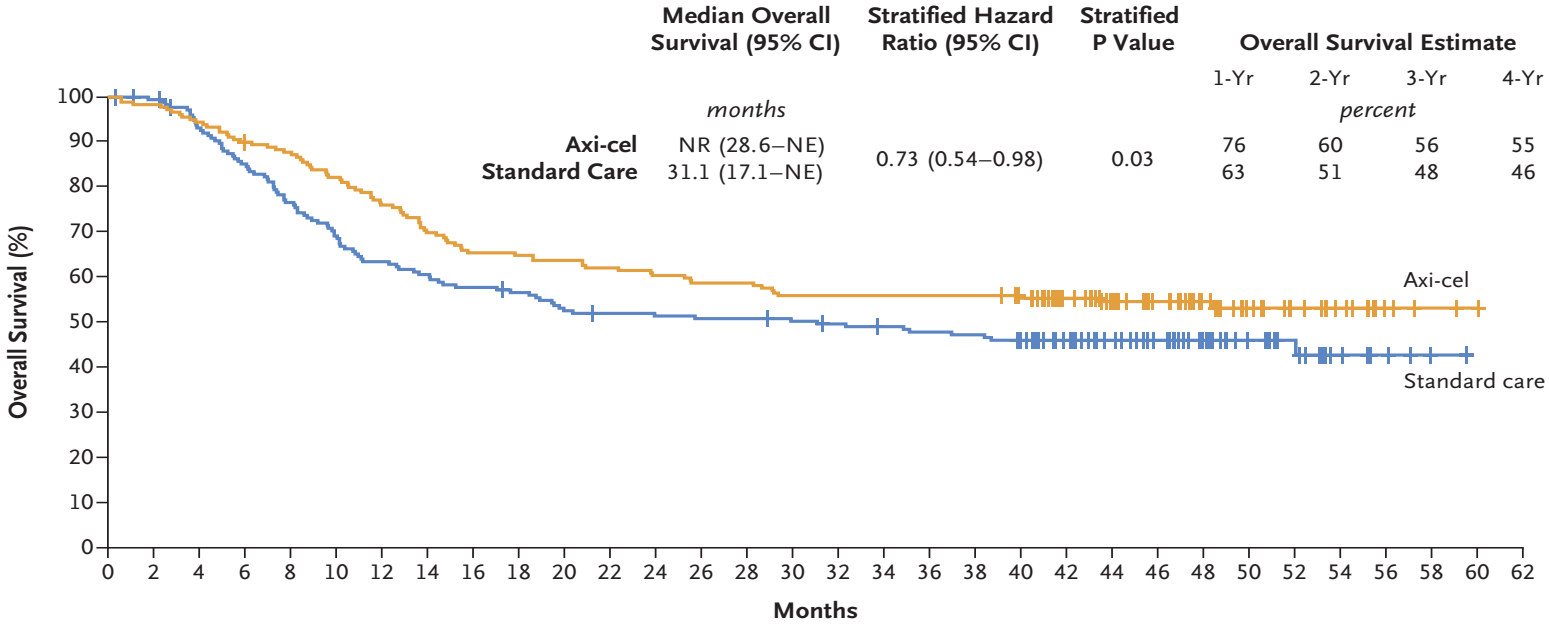
ZUMA-7 Improved OS with CAR-T as second line therapy



Westin J et Al. N Eng J Med 2023

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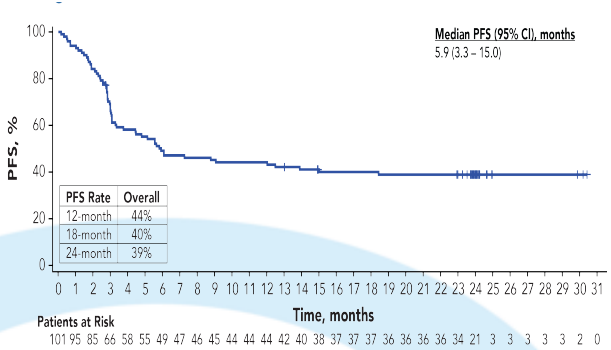
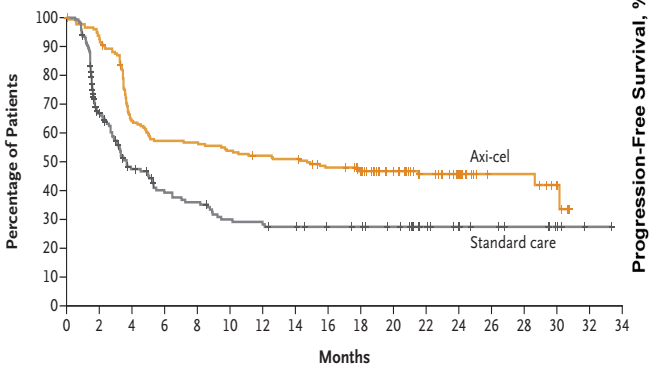
Earlier use of CART may improve outcome

ZUMA-1



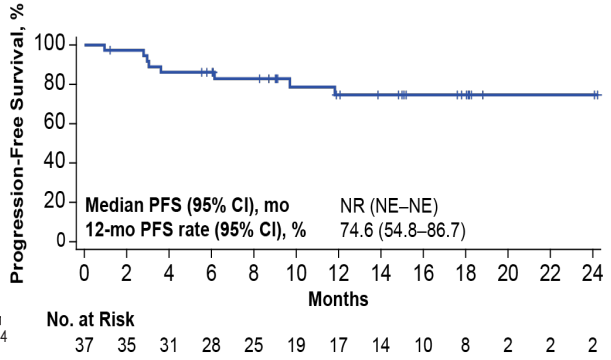
Median PFS 5.9 months

ZUMA-7



Median PFS (axi-cel arm): 14.6 months

ZUMA-12



Median PFS: Not reached

Locke et al. *Lancet Oncol* 2018, Locke et al. *N Eng J Med* 2021, Neelapu ASH Meeting Abstracts 2021

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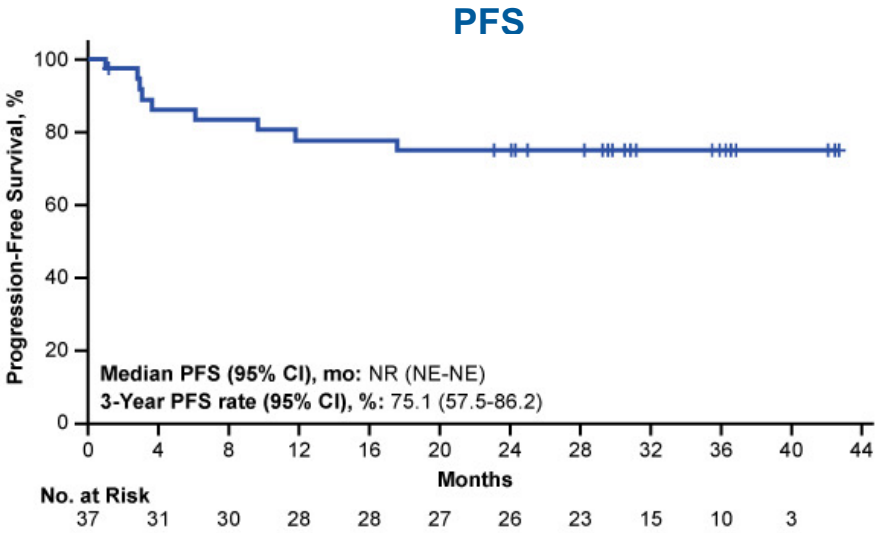
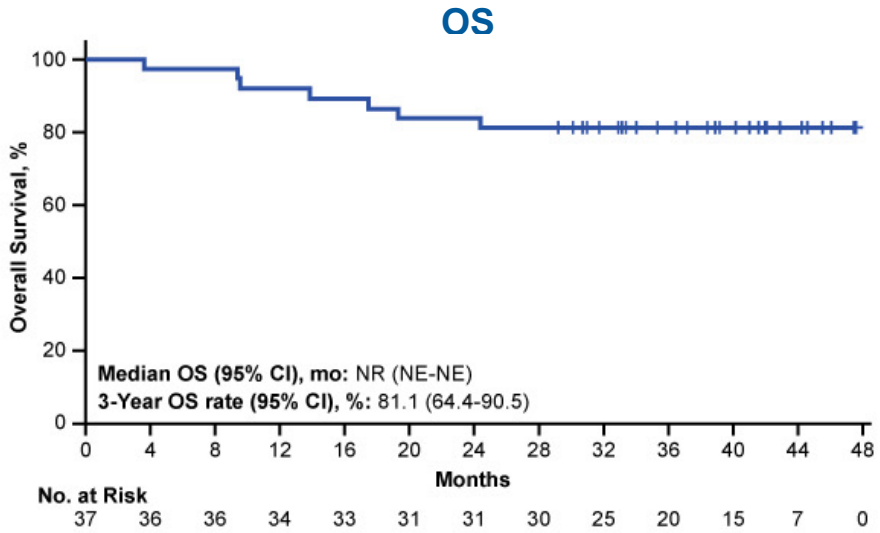
ZUMA-12 Axi-Cel as Frontline Therapy for High Risk DLBCL: 3-year follow up





- Medians for PFS and OS were not reached in efficacy-evaluable patients
  - Among patients who achieved a CR as best response, the 3-year PFS and OS rates **were 84.4%** (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

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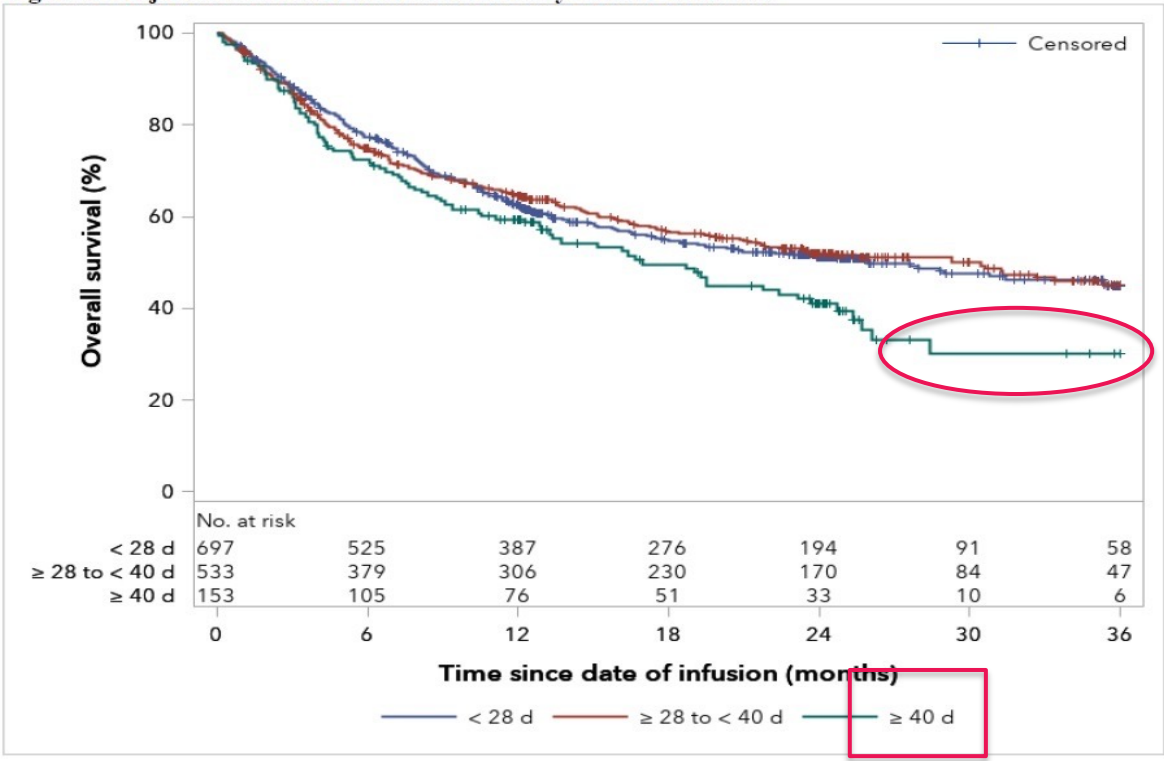
Impact of CAR-T infusion waiting times in DLBCL: CIBMTR analysis (> 1300 pts)

Figure 1: Adjusted curves for overall survival by vein-to-vein time



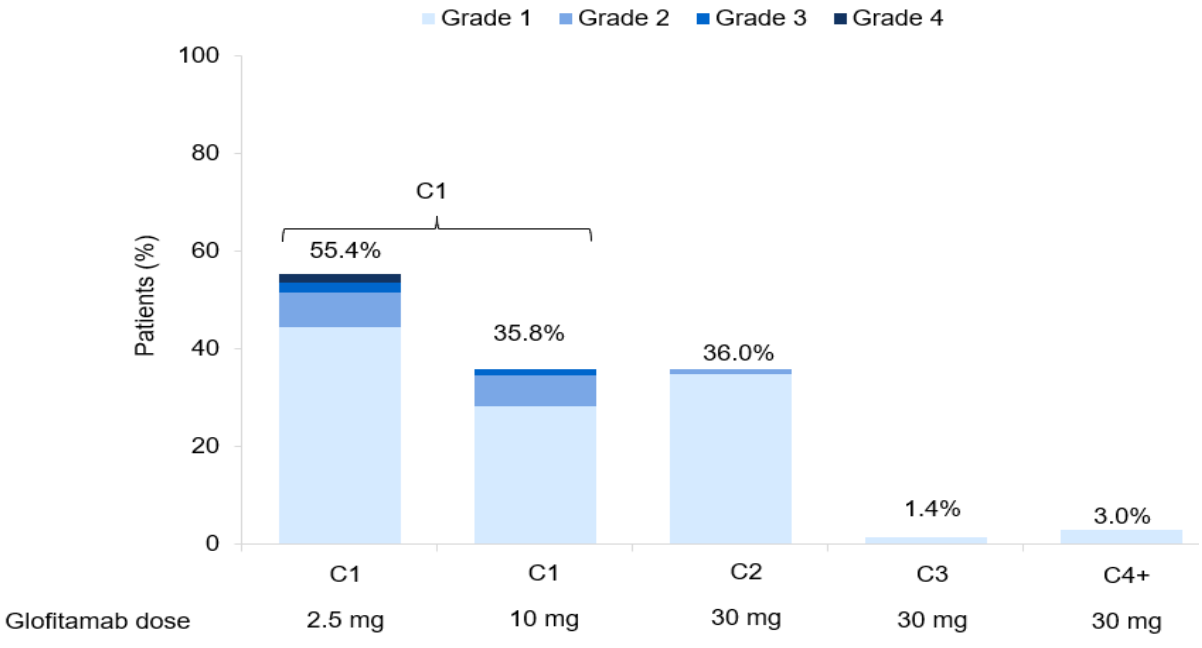
Locke et al ASH Meeting Asbtract 2022: 3345

Bispecific antibodies for LBCL

What have we learned about BiAbs in lymphomas?

- They can cause CRS (mostly during C1)
- Neurotoxicity is unusual
- Efficacy is dose dependent
- Step up dosing mitigates toxicity and may spare need for admission

CRS events occur early: Analysis of Glofitamab Phase 2 Pivotal Cohort



Dickinson M al. *N Eng J Med* 2022.

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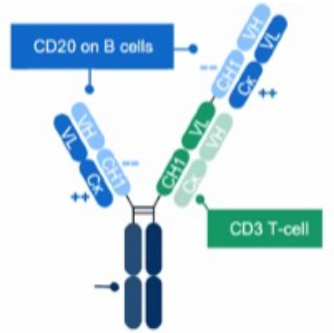
Bispecific Abs: FDA approvals R/R LBCL

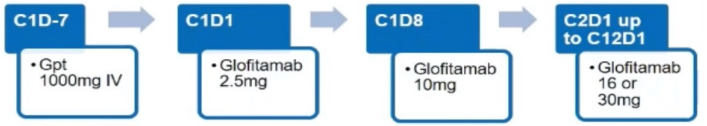
Glofitamab

FDA approved June 2023



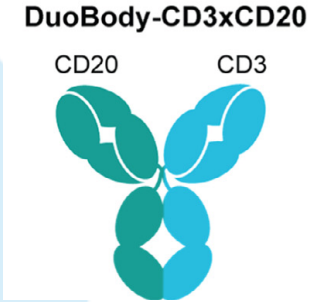
Treatment schedule

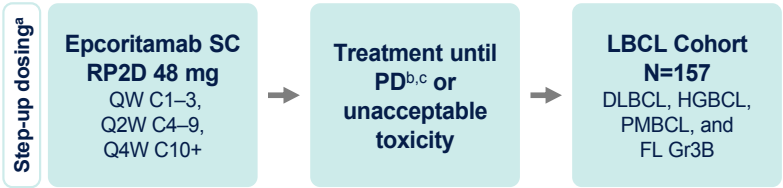
- 1000mg Gpt 7 days prior to glofitamab administration
- Glofitamab IV step-up doses on C1D1 and D8 and at target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg)
- Cycle 1 was 14-days long; glofitamab was given Q3W thereafter for up to 12 cycles



Epcoritamab

FDA approved May 2023





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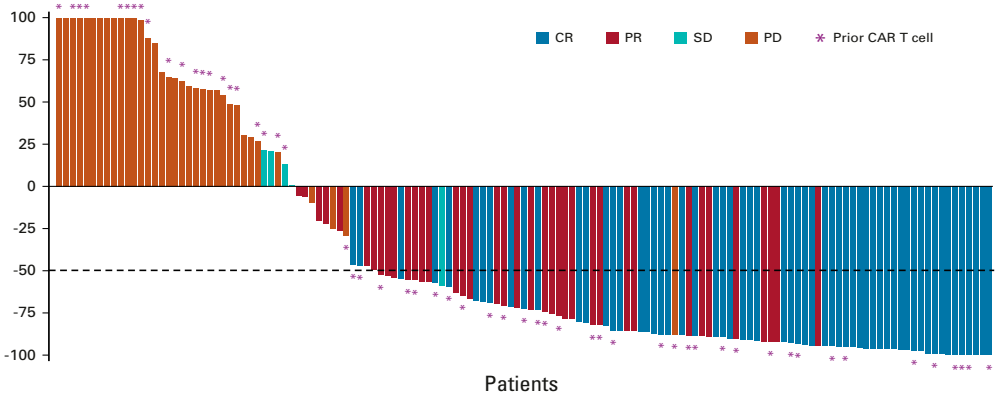
Epcoritamab for R/R DLBCL: Phase 2 pivotal study

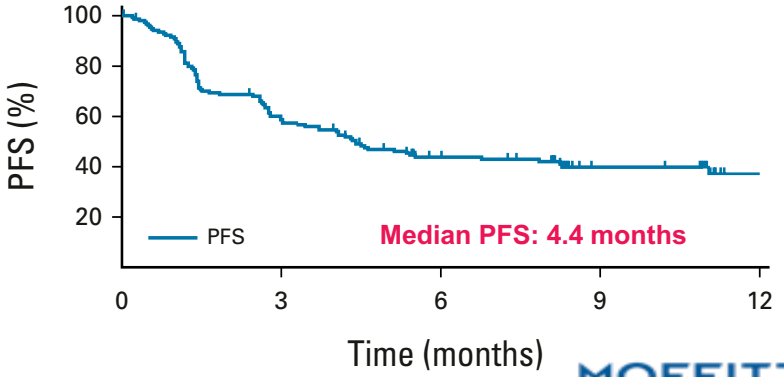
Baseline Characteristics

N= 157 pts
Unlimited treatment (SC)
Median lines: 3 (2-11)
Primary refractory: 61%
Prior CAR-T: 38.9%
Prior auto HCT: 20%

Results

Median f/u: 10.7 months
ORR= 63%
CR= 39%
PFS in CR pts at EOT: Not reached
Median PFS= 4.4 months. Not reached in MRD-
CRS all (G≥3)= 49.7% (2.5%) Mainly during C1





Thieblemont at Al. EHA Congress 2022; Thieblemont et Al. J Clin Oncol 2022

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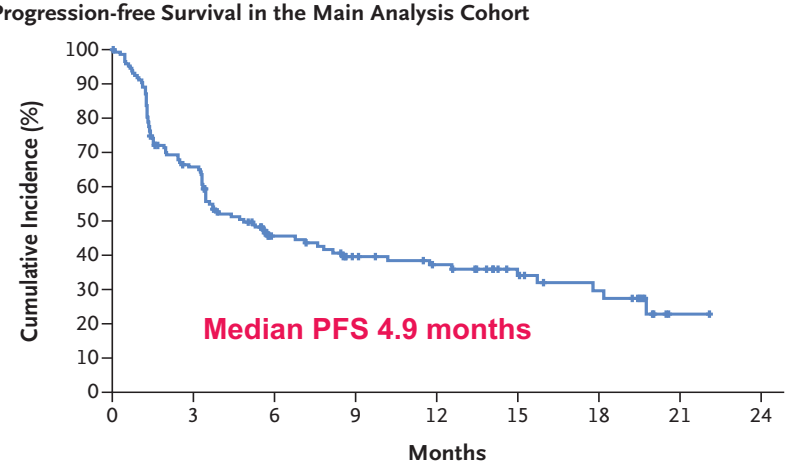
Glofitamab for RR Large B-cell Lymphoma (3L): Phase 2 Pivotal Results

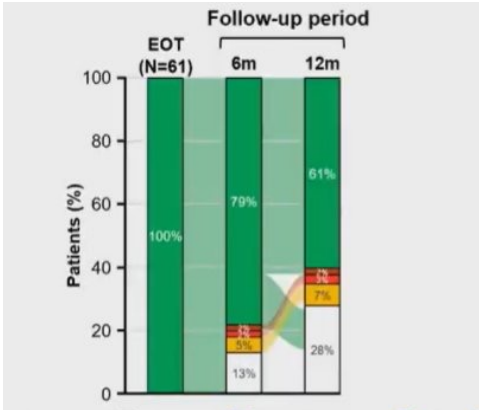
Baseline Characteristics

N= 155 pts
Time limited therapy (12 cycles IV with pretreatment obinutuzumab)
Median lines: 3 (2-7)
Primary refractory: 58%
Prior CAR-T: 33%
Prior auto HCT: 18%

Results

Median f/u: 12.6 months
ORR= 52%
CR= 39%
PFS in CR pts at EOT: Not reached
Median PFS= 4.9 months
CRS all (G≥3)= 63% (4%) Mainly during C1





Dickinson M et Al. *N Eng J Med* 2022.

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Efficacy of FDA approved CAR-T and BiAbs in R/R LBCL

	ZUMA-1	TRANSCEND	JULIET	EPCORE	GO
Product	**Axi-Cel**	**Liso-Cel**	**Tisa-Cel**	**Epcoritamab**	**Glofitamab**
Median F/U	60 months	24 months	40.3 months	10.7 months	12.6 months
ORR	83%	75%	52%	63.1%	52%
CR	54%	53%	40%	38.9%	39%
PFS	5.9 months	6.8 months	2.9 months	4.4 months	4.9 months
OS	25.8 months	27.3 months	11.1 months	NR	8.9 months

Neelapu et Al. *Blood* 2023, Abramson et Al. *Blood* 2023, Schuster et Al. *Lancet Oncology* 2021, Thieblemont at Al. *J Clin Oncol* 2022, Dickinson M et Al. *N Eng J Med* 2022.

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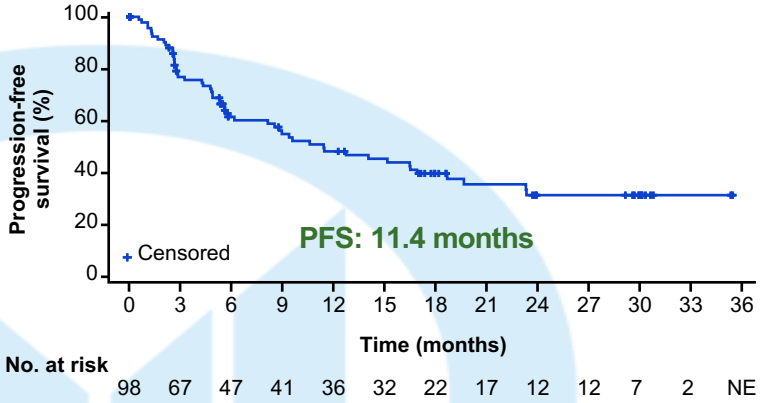
Combination of BiAbs seems to increase efficacy

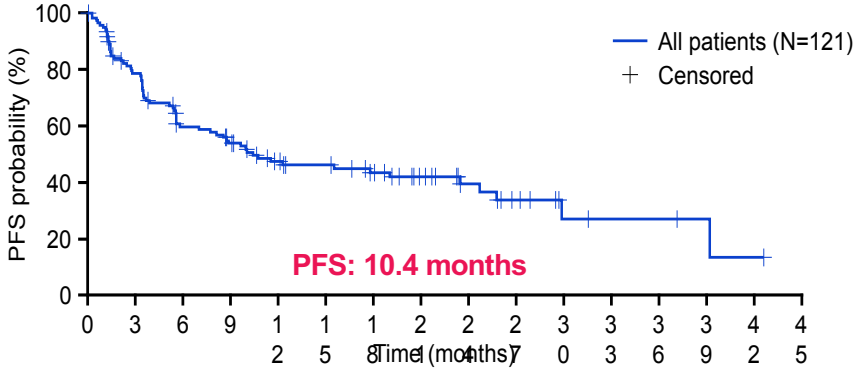
Mosunetuzumab - Polatuzumab

N= 98. Median F/U: 23.9 months
Median lines: 2 (1-8)
Post CAR-T: 35.7%
ORR= 63.5% CR= 51%



Glofitamab - Polatuzumab

N= 121. Median F/U: 20.4 months
Median lines: 2 (1-7)
Post CAR-T: 22.4%
ORR= 80.2% CR= 59.2%



Budde E, Chavez JC et Al. *Nat Medicine* 2023, Hutchings M et Al. ASH Meeting 2023

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Key Immune-Related Toxicities: CAR-T and BiAbs

	ZUMA-1	TRANSCEND	JULIET	EPCORE	GO
Product	**Axi-Cel**	**Liso-Cel**	**Tisa-Cel**	**Epcoritamab**	**Glofitamab**
CRS (all grades)	93%	39%	58%	47.9%	63%
CRS $\geq$ 3	13%	1%	22%	2.5%	4%
ICANS (all grades)	64%	23%	21%	6.4%	8%
ICANS $\geq$ 3	28%	10%	12%	0.6%	3%

Neelapu et Al. *Blood* 2023, Abramson et Al. *Blood* 2023, Schuster et Al. *Lancet Oncology* 2021, Thieblemont at Al. *J Clin Oncol* 2022, Dickinson M et Al. *N Eng J Med* 2022.

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Sequencing: CAR-T or BiAbs

BiAbs are very effective post CAR-T relapse

Glofitamab

N Pts: 51 (33%)
ORR: NR
CR: 32%

Epcoritamab

N pts: 61(38.9%)
ORR: 54.1%
CR: 34.4%

Odronextamab

N pts: 41 (~33%)
ORR: 48%
CR: 30%

Dickinson M et Al. *N Eng J Med* 2022. Thieblemont C at Al. *J Clin Oncol* 2022, Crombie J at Al. ASH Meeting 2023

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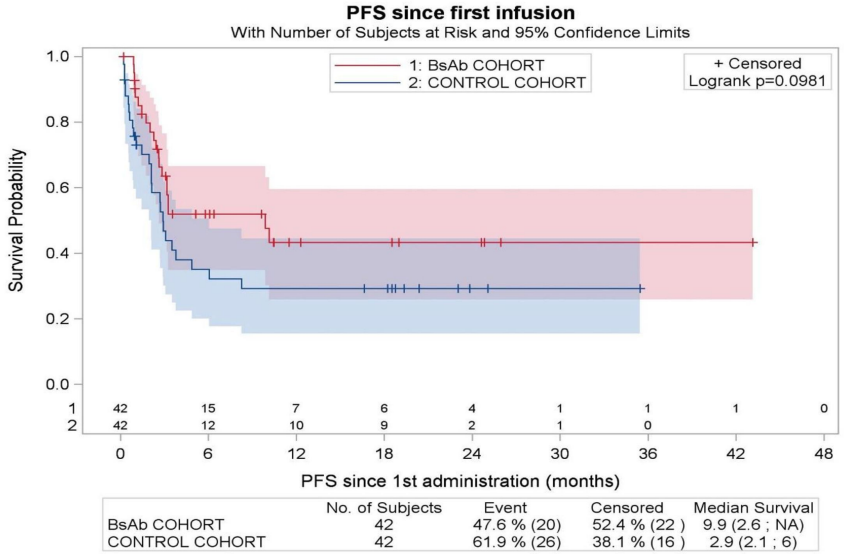
CAR-T is also active post BiAbs progression

Multicenter study (Europe)
N= 47 pts.
Median lines 2 (prior to BiAbs)
CART: Axi-cel (47%), tisa-cel (43%), liso-cel (11%)
ORR: 83%
CR: 43%
Response independent to prior BiAbs response
PFS= 6.6 months



Iacoboni G at Al. ASH Meeting Abstracts 2023

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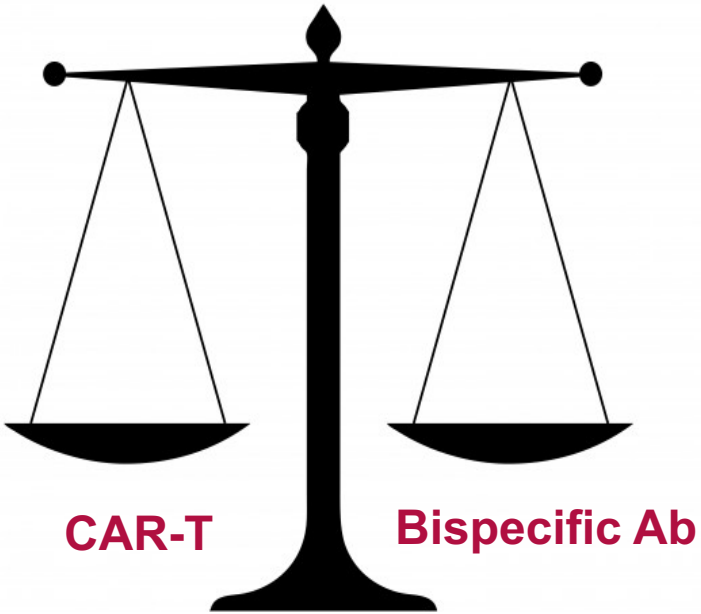
Choosing CAR-T vs BiAbs

- Curative: Long-term efficacy data (ZUMA-1: 5-years)
- OS benefit over SOC (ZUMA-7, TRANSFORM)
- One time treatment
- RWE confirms efficacy
- Higher frequency/severity CRS/ICANS
- Logistics (distance, caregiver)
- Manufacturing time/failure
- Other toxicities (cytopenias, infections)



- “Off the shelf”
- Similar efficacy
- Lower risk/severity CRS/ICANS
- Combination seem more feasible and effective (mosun-pola)
- Curative? Unclear
- No RWE data (yet)
- Repetitive dosing and indefinite (Epcoritamab)
- Specialized training still required

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